

appropriate eye care. It is less expensive to provide preventive care than to support subsequent disability and its associated personal and social suffering.

Using the results of these clinical trials, a treatment plan for diabetic retinopathy has been designed and proved medically and cost effectively. The trials have shown that most patients with diabetes go blind because they are treated too late. They must be evaluated early to reap the benefits of these studies.

PAUL E. TORNAMBE, MD  
La Jolla, California

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## Retinitis Pigmentosa—New Advances in Ophthalmic Genetics

RETINITIS PIGMENTOSA is both clinically and genetically heterogeneous. It comprises a group of X-linked autosomal recessive and autosomal dominant diseases that affect 50,000 to 100,000 people in the United States, with the incidence ranging from 1 in 3,000 to 1 in 7,000. The early symptoms of retinitis pigmentosa include night blindness and a loss of peripheral fields of vision. As the condition progresses, visual acuity and central vision are also affected. Examination of the fundus reveals attenuated retinal vessels, bone-spicule pigment around the periphery of the retina, and occasionally pale optic discs.

Molecular biologic studies have defined the genetic defects for at least some of the persons and families who have autosomal-dominant retinitis pigmentosa. Most of the mutations discovered to date are the result of changes in a single nucleotide in the rhodopsin gene. Different families may carry different mutations, but affected members of the same family carry the same dominantly inherited mutation. These mutations lead to single amino acid changes in the rhodopsin molecule. The first mutation discovered was a C-to-A base change in the 23rd codon of the rhodopsin gene that resulted in a substitution in the 23rd amino acid of histidine for proline. This mutation was denoted as the proline-23-histidine mutation. In a recent report of 161 unrelated patients with autosomal-dominant retinitis pigmentosa who were screened, 26 (24%) were found to carry a point mutation in the rhodopsin gene. This study described 13 different mutations at 12 different amino acid positions. Research is under way to uncover the molecular defects in the rest of these patients by exploring the possibility of defects in other retinal and photoreceptor genes, such as arrestin (also known as S antigen), transducin, peripherin, and others.

Many investigators have attempted to correlate observed genetic heterogeneity with variability in the clinical severity and prognosis of autosomal-dominant retinitis pigmentosa. Initial observations suggested that patients with certain muta-

tions, such as proline-23-histidine, threonine-58-arginine, glycine-182-serine, and threonine-17-methionine, may have better long-term prognoses than others for the retention of good visual acuity and functional peripheral visual fields. In patients with the proline-347-leucine mutation, there is an increased likelihood of more severe functional impairment. The age of onset and severity of the disease, however, may vary substantially among patients with the same mutation.

How can these new discoveries be used to diagnose and treat patients with retinitis pigmentosa? Molecular genetics, in conjunction with a review of family history and careful clinical examination, can in some cases determine whether a person with a family history of autosomal-dominant retinitis pigmentosa is carrying the disease gene while asymptomatic. This information can assist persons in making career and family choices. The application of further clinical and basic research will one day help to decipher the biochemical basis for retinal degeneration in retinitis pigmentosa, which we hope will lead to a rational basis for treating the disorder. Further research is also required to determine the molecular defect in the great majority of persons with dominantly inherited retinitis pigmentosa, as well as in patients with the autosomal recessive and X-linked type. Patients with this disorder optimally should be referred to centers with experience in its diagnosis and treatment and be enrolled in clinical studies.

VINH TAN TRAN, MD, PhD  
Los Angeles, California

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## Current Therapy for Disorders of the Optic Nerve

OPTIC NEURITIS is characterized by subacute unilateral loss of central vision in patients younger than 40 years, associated with pain on eye movement, diminished pupillary response, and optic disc edema in about 40%. It may be associated with systemic disorders such as systemic lupus erythematosus and syphilis and may be mimicked by parasellar tumors. Most cases are idiopathic, in which there may be a strong association with multiple sclerosis. The value of corticosteroid therapy in idiopathic optic neuritis has not been proved. Early reports indicated that treatment reduced pain and increased the speed of visual recovery but did not appreciably affect the final level of visual acuity. Most neuro-ophthalmologists have treated only those patients with severe pain or with a definitive need for the rapid recovery of vision, such as patients with severe loss of vision, or only one functional eye. The recent national multicenter clinical trial of systemic corticosteroid use in optic neuritis (Optic Neuritis Treatment Trial) showed that oral prednisone therapy alone had no beneficial effect and was associated with an increased risk of recurrence; study investigators have therefore recommended against its use. An initial course of intravenous methylprednisolone sodium succinate, however, followed by oral prednisone was beneficial in patients with visual acuity worse

than 20/40. In patients with more severe vision loss, consideration should be given to this therapy.

Nonarteritic anterior ischemic optic neuropathy, an infarct of the optic nerve head, is the most common cause of acute optic neuropathy in patients older than 50. It presents as acute, painless, unilateral loss of vision associated with impaired pupillary response and optic disc swelling. It typically occurs as a single episode but may progress over a period of weeks in 20% to 30% of cases. Recent studies suggest that optic nerve sheath decompression, a surgical procedure in which cerebrospinal fluid is released through an incision into the subarachnoid space surrounding the optic nerve, may reduce permanent optic nerve damage in the progressive form of nonarteritic anterior ischemic optic neuropathy. The procedure, which theoretically works by reducing intrasheath pressure, allowing for improved blood flow to the optic nerve head, has proved effective in chronic optic disc edema from increased intracranial pressure (most commonly pseudotumor cerebri). Its use in nonarteritic anterior ischemic optic neuropathy, however, is controversial. A recent series of reports indicated notably improved vision after optic nerve sheath decompression in a high percentage of patients, but several investigators have presented data that do not corroborate this success. A multicenter clinical trial, the Ischemic Optic Neuropathy Decompression Trial, has recently been funded by the National Eye Institute to evaluate the effectiveness of this therapy; recruitment of some 300 patients over 18 months was started in 1992.

ANTHONY C. ARNOLD, MD  
Los Angeles, California

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## Graves' Ophthalmopathy

THE DIAGNOSIS OF Graves' ophthalmopathy is purely clinical and is unrelated to the systemic thyroid state. Although most patients have hyperthyroidism, euthyroid patients or those with hypothyroidism also present with ocular symptoms. Orbital computed tomographic scans are helpful in predicting possible loss of vision but are rarely necessary for the diagnosis of Graves' ophthalmopathy. Although some form of symptomatic ocular involvement is present in at least 31% of patients with Graves' thyroid disease, the ophthalmopathy may occur, both in timing and severity, independent of the thyroid disease.

Data on the natural history of Graves' ophthalmopathy remain scarce. Most investigators agree that the disease is self-limiting and runs a course of exacerbations and spontaneous remissions, becoming stable within 18 to 36 months. Hence, ongoing collaboration among primary care physicians, endocrinologists, and ophthalmologists is paramount for optimal patient care.

There is no known effective treatment to prevent the development of Graves' ophthalmopathy. Our efforts remain directed at palliating symptoms. Managing the thyroid dysfunction in these patients is the first logical step in the treat-

ment of Graves' ophthalmopathy, but the disorder may continue to progress.

When considering treatment, patients can be divided into three major categories: those with active vision-threatening optic neuropathy, those with active nonvision-threatening ophthalmopathy, and those with chronic stable ophthalmopathy. Patients with acute Graves' optic neuropathy require urgent treatment to prevent permanent loss of vision. The longer treatment is delayed, the less adequate visual recovery will be. Corticosteroid therapy is generally the first line of treatment. In patients who cannot tolerate corticosteroids, cyclosporine has been recently suggested as an alternative or adjunct to corticosteroids, but its effects on ophthalmopathy are not well documented and the side effects are potentially serious. For patients who have a recurrence of optic neuropathy with tapering of their corticosteroid regimen or for those who do not respond to or simply cannot tolerate corticosteroid therapy, either orbital decompression or orbital irradiation is indicated. Orbital decompression remains a successful treatment of optic neuropathy, whereas orbital radiotherapy remains controversial because of the risks of dry eye and radiation retinopathy associated with low-dose irradiation. In addition, the risk of inducing tumors is unknown.

For patients with nonvision-threatening acute ophthalmopathy, symptomatic treatment and expectant follow-up are indicated. Artificial tears, lubricants, night-time patching of the eyelids, elevation of the head of the bed, and wrap-around glasses are helpful treatments. No controlled trials have been done that demonstrate the efficacy of corticosteroid therapy or irradiation in altering the natural history of the ophthalmopathy or in improving proptosis or diplopia once the disease has become stable. The risk of corticosteroid use or irradiation must therefore be weighed against the short-term improvement in active inflammation. If steroids are prescribed, they should be given over a course of two to three weeks, with rapid tapering to avoid prolonged treatment even if inflammation recurs.

Once fibrosis has developed in patients with chronic stable thyroid ophthalmopathy, neither corticosteroid nor radiation therapy has a role because active inflammation is not present. For these patients, surgical reconstruction may be considered. Most surgeons agree that the reconstructive operations should be done in sequence with orbital decompression, followed by the correction of double vision, and, finally, an eyelid operation. The surgical procedure must be tailored to the special needs of each patient. Cosmetic orbital decompression in the absence of functional diplopia must be undertaken with caution because diplopia will develop in 30% to 50% of patients after surgical decompression.

An often overlooked yet equally important component of Graves' disease is the psychosocial stress associated with the disease. Graves' disease often has substantial economic and social effects, as patients are commonly in their wage-earning years and, in some cases, are unable to do their jobs because of their visual symptoms. The cosmetic disfigurement produced by ophthalmopathy may cause a reactive depression, placing stress on the family. These patients may be referred to a support group through the National Graves' Disease Foundation (11111-2A San Jose Blvd, Suite 123, Jacksonville, FL 32223).

DENISE F. DUDLEY, MD  
JAMES C. ORCUTT, MD, PhD  
Seattle, Washington